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EXAMINER
FURMAN, K

LEGAL AFFAIRS DEPT.
GENETICS INSTITUTE, INC.
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ART UNIT	PAPER NUMBER
1814	10

DATE MAILED: 02/05/93

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 1-4-93 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☑ Notice re Patent Drawing, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1-25 are pending in the application.
   Of the above, claims 1-5, 10-12 and 20-25 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 6-9 and 13-19 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☑ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).
12. ☑ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☑ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 9-89)

07/800,364

15. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-5, 10-12 and 20-25, drawn to BMP-8 proteins, pharmaceuticals and methods of treatment, classified in Class 514, subclass 12; and Class 530, subclass 350.

II. Claims 6-9 and 13-19, drawn to DNAs, host cells and methods of producing recombinant BMP-8, classified in Class 536, subclass 27; Class 435, subclass 240.2+, depending upon the nature of the cell, and subclass 69.1.

16. The inventions are distinct, each from the other because of the following reasons:

The inventions of Group II and Group I are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (M.P.E.P. § 806.05(f)). In the instant case the protein can be made by purification from natural sources using convention purification techniques or combinations of purification techniques including, ion exchange chromatography, hydrophobic interaction chromatography, thiophilic adsorption chromatography, immunoaffinity purification techniques, ultrafiltration, density gradient ultracentrifugation, reverse-phase HPLC and/or other conventional purification techniques. Additionally, the DNA and products containing the DNA of Group II are chemically distinct compounds having separate status in the art as show by their diverse classification and the DNA and host cells can be used other than to make the protein, such as to make additional DNA for use as a probe to detect and/or obtain the same or similar nucleic acid molecules.

17. If Group I is elected, Claims 1, 2, 10 and 20-24 are generic to a plurality of disclosed patentably distinct species comprising (1) species a) of claim 1; (2) species b) of claim 1; (3) species c) of claim 1; (4) species

d) of claim 1; (5) species e) of claim 1 (i.e. the mature protein also in claims 4, 12 and 25); (6) the species of claim 5, i.e. the intact protein plus presequence) and (7) the human BMP of ATCC #75010 (claims 3 and 11). These species are distinct one from the other because the are drawn to different amino acid sequences required and/or proteins of different size which include portions of sequence not included in the other species which requires searching not required for the other species and therefore requires a separate field of search though they may be classified together. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

18. If Group II is elected, Claims 6, 13 and 17 are generic to a plurality of disclosed patentably distinct species comprising (1) species a) of claim 6; (2) species b) of claim 6; (3) species c) of claim 6; (4) species d) of claim 6 encoding the intact protein plus presequence (also in claims 7, 14 and 19); (5) species e) of claim 6 (i.e. encoding the mature protein also in claims 8 and 15); (6) the DNA of ATCC #75010 including introns (claims 9, 16 and 18). These species are distinct one from the other because the are drawn to different DNA sequences required and/or DNAs of different size which include portions of sequence not included in the other species which requires searching not required for the other species. Applicant is required under 35 U.S.C. § 121 to elect a single disclosed species, even though this requirement is traversed.

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the

examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. § 103 of the other invention.

19. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and because the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

20. During a telephone conversation with Ellen Kapinos on 1-15-93 a provisional election was made with traverse to prosecute the invention of Group II, claim 6-9 and 13-19 and the species of (4) above which reads upon 6, 7, 14 and 19. However, since no prior art was found for the elected species, all the species were searched and examined on the merits in Group II. Affirmation of this election must be made by applicant in responding to this Office action. Claims 1-5, 10-12 and 20-25 are withdrawn from further consideration by the Examiner, 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

21. Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed.

22. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

23. The following is a quotation of the first paragraph of 35 U.S.C. § 112:
The specification shall contain a written description of the invention,

and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

24. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention. The written description is inadequate because the amino acid sequence of bovine BMP-8 is stated in the last line of p. 32 as corresponding to that of SEQ ID NO: 13. However, this in incorrect for two reasons: (1) SEQ ID NO:13 is a nucleic acid sequence (even though the amino acid sequence is shown); and (2) both SEQ ID NO:13 and SEQ ID NO: 14 correspond to the human BMP-8 nucleic acid and amino acid sequences, respectively, not the bovine amino acid sequence shown in Table 4. Since none of the SEQ ID numbers of the specification correspond to the bovine BMP-8 amino acid sequence of Table 4 and since the bovine amino acid sequence differs from the human sequence at only three amino acid positions, it is suggested that the specification refer to the bovine BMP-8 amino acid sequence of Table 4 as corresponding to the sequence of SEQ ID NO: 14 from amino acid position number 31 through position 142 wherein Met at position 97 is replaced with Leu, Asn at position 100 is replaced with His and Lys at position 137 is replaced with Arg.

The written description is also inadequate because numerous other references to SEQ ID numbers are confusing. At numerous places in the specification particular amino acid or nucleic acid position numbers of a Figure are referred and a particular SEQ ID NO: in parenthesis immediately follows the reference to the Figure but it is not clear whether the sequence of the SEQ ID NO: is the equivalent of the entire sequence of the Figure or the equivalent of the sequence corresponding to the range of positions in the Figure. For example, see line 34 of p. 2 (which is not numbered as page 2) through line 1 of p. 3 and lines 4 and 5 of p. 4. Additionally, the position numbers of the Figure do not correspond to the numbers of the SEQ ID NO:.

Therefore, if applicant refers to both the Figure or Table and the SEQ ID NO: the positions should be specifically noted for each where the sequence is less than the full sequence of the SEQ ID NO.

25. Claims 6, 13 and 17 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to where the DNA of the claims encodes a protein having at least the sequence of amino acids that is encoded by nucleotide #430 through #843 of Figure 2. See M.P.E.P. §§ 706.03(n) and 706.03(z). The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). The scope of the claims is not reasonably correlated with the scope of enablement of the instant specification because the claims are directed to DNAs which encode a BMP-8 protein, which proteins are defined in the specification as having the ability to stimulate, promote or otherwise induce bone and/or cartilage formation (see p. 3, lines 2-4 and line 24 of p. 4 through p. 6 of the specification), but are limited to merely comprising one of sequences a), b) or c) of the Markush grouping of claim 6. The DNAs of species a), b) and c) of claim 6 have **not** been shown to encode by themselves (i.e., absent the other coding regions of that set forth in sequence e) of claim 6), to encode a BMP-8 protein having the activities described and would not be expected, by themselves, to encode peptides having this activity since they lack substantial portions of the mature protein. The DNAs comprising at least one of species a), b) and c) are not limited to encoding a protein of particular size which occurs naturally in the source it was obtained from and are open to include any possible addition DNA sequence at either end. However, since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge

of the ways in which the proteins' structure relates to its function. However, the knowledge that may be gleaned from the known members of the BMP family of proteins is limited and precise regions critical to activity do not appear to have been known. Further, it would clearly require undue experimentation to determine the extremely broad scope encompassed by the claims of other non-homologous amino acid sequences which nevertheless have sufficient tertiary structure similarity or other structural similarities sufficient to impart BMP-8 activity to use for the parts of the BMP-8 protein which are not encoded by each of species a), b) or c).

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity/utility are limited in any protein and the result of such modifications representative of the essentially infinite the scope broadly set forth is unpredictable based on the instant disclosure and the prior art. Further, one skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. Additionally, the specification fails to provide guidance with regard to (A) the general tolerance to modification and extent of such tolerance; (B) specific positions and regions of the sequence(s) which can be predictably modified; (C) which regions are critical to activity; (D) what fragments, if any, can be made which retain the biological activity of the intact protein; and (E) the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful. Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546

(Bd. Pat. App. & Int. 1986).

In addition to the scope set forth above by the Examiner as being reasonably correlated with the enablement of the specification, some additional or other modifications which could be made and used with a reasonable expectation of success, or which would otherwise not require undue experimentation, would also be obvious (e.g. DNAs encoding BMP-8 proteins with minor conservative amino acid substitutions). The specification, however, does not appear to provide antecedent basis for the language of limitations which would encompass all such obvious modifications either because such obvious modifications are not specifically defined or classed in the instant specification, or because it cannot be readily determined or succinctly stated which modifications are so obvious. Therefore, it is expressly noted for the record by the Examiner that limiting the scope of the claims so as to be included within the scope set forth above by the Examiner as enabled should not preclude applicant(s) from protecting under the doctrine of equivalents such additional or other modifications which would also be obvious.

26. Claims 17 and 18 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited wherein the protein recovered in step (b) is the one encoded by the coding regions of the DNA sequence of in step (a) in both claims 17 and 18, and in claims 17 wherein the sequence is either that set forth in d) or e) or DNAs which encode the same protein(s) encoded by the DNAs of species d) of e). See M.P.E.P. §§ 706.03(n) and 706.03(z). The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). However, the instant claim does not bear a reasonable correlation with the scope of the enablement because step (b) broadly includes the recovery of any protein having the functional limitations of the ability to induce cartilage and/or bone formation which may be in addition to or even instead of the protein produced by the DNA set forth in step (a). However, applicants have not enabled the extremely broad scope representative of all proteins having

this function which may even include many other proteins structurally unrelated to the BMP family of proteins nor representative of all possible modifications of the proteins of the BMP family since the amino acid sequence of a given protein determines its structure/function and the sequence information contained in the sequences of the proteins of the BMP family is limited and because it is not routine in the art to screen for **multiple** substitutions (i.e. beyond that which can be reasonably deduced from differences between homologous proteins having the same structure) to obtain functionally equivalent molecules. Thus, undue experimentation would be required to support the broad scope of step (b) of the claim. Claim 17 should be limited to the DNA of species d) or e) of as set forth in claim 6 or DNAs which encode the same protein(s) encoded by the DNAs of species d) of e) for the reasons discussed above in the immediately preceding rejection under 35 U.S.C. § 112, first paragraph, regarding the scope of claims 6, 13 and 17.

27. The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for the claimed invention. It is apparent that ATCC #75010 set forth in claim 9 and referred to on p. 34 of the instant specification is required to practice the claimed invention because the precise sequence of the DNA encoding BMP-8 of ATCC #75010 is not elsewhere disclosed and this DNA is specifically claimed in claims 9 and 18. As a required element it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of ATCC #75010. See 37 C.F.R. 1.802.

The specification does not provide a repeatable method for obtaining ATCC #75010 and it does not appear to be readily available material. Deposit of ATCC #75010 would satisfy the enablement requirements of 35 U.S.C. § 112. If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who

is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty (as already set forth on p. 34 of the instant specification) and that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements. See 37 C.F.R. 1.808.

28. Claims 9 and 18 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

29. Claims 6-8, 13-15 and 19 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6-8 and 19 are indefinite because particular amino acid or nucleic acid position numbers of a Figure are referred and a particular SEQ ID NO: in parenthesis immediately follows the reference to the Figure but it is not clear whether the sequence of the SEQ ID NO: is the equivalent of the entire sequence of the Figure or the equivalent of the sequence corresponding to the range of positions in the Figure. See species d) and e) of claim 6 and claims 6-8. Additionally, the position numbers of the Figure do not correspond to the numbers of the SEQ ID NO:. Therefore, if applicant refers to both the Figure or Table and the SEQ ID NO: the positions should be specifically noted for each where the sequence is less than the full sequence of the SEQ ID NO. However, to avoid redundancy it is suggested that the claims refer only to the SEQ ID NO: and any specific positions thereof rather than to the Figures.

30. Claim 19 is objected to because step (a) contains no reference to a SEQ ID NO: which is required (see 37 CFR § 1.821(d)).

31. 35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

32. Claims 6, 9, 13 and 16 are rejected under 35 U.S.C. § 101 because the claimed invention is directed to non-statutory subject matter. The DNAs of species a), b) and c) of claim 6 and of claim 9 and the host cells, as claimed, has the same characteristics and utility as that found in nature. To overcome this rejection the Examiner suggests the amendment of the claims to include purity limitations which would distinguish the characteristics and utility of applicant's DNA as enabled in the specification from the utility of the DNA it exists in nature. The DNAs of claims 6 and 9 are not limited to having been isolated and the open-ended term "comprising" in claim 6 leaves the claim open to include the other naturally occurring sequence and ingredients associated with these DNAs. The species of claim 9 includes the naturally occurring introns and is not limited to having been isolated. With respect to the host cells of claims 13 and 16, regardless of whether the claims are amended to wherein the DNA is isolated, a host cell merely limited to being transformed with such isolated DNA, would still encompass the natural cells containing the genes since product-by-process limitations would not distinguish over the same products occurring naturally. It is noted that the other products of the claims are not included in the instant rejection because the DNAs are limited with respect to purity and/or inherently exclude naturally occurring intron regions. For relevant case law see Farbenfabriken of Elberfeld Co. v. Kuehmsted, 171 Fed. 887, 890 (N.D. Ill. 1909) (text of claim at 889); Parke-Davis & Co. v. H.D. Mulford Co., 189 Fed. 95, 103, 106, 965 (S.D.N.Y. 1911) (claim 1); and In re Bergstrom, 427 F.2d 1394, 1398, 1401-1402 (CCPA 1970).

33. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. The reference of Oppermann et al discloses similar osteogenic proteins and some DNA sequences thereof with their amino acid sequences aligned along with other homologous proteins having somewhat different function/utility (see Figure 18).

34. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1814.

35. Papers relating to this application may be submitted to Group 1810 by facsimile transmission. Papers should be faxed to Group 1810 via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center number is (703) 308-4227. Papers may be submitted Monday-Friday between 8:00 am and 4:45 pm (EST). Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

36. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Keith Furman whose telephone number is (703) 308-3453. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

January 28, 1993

Keith C. Furman

KEITH C. FURMAN, Ph.D.
PATENT EXAMINER
ART UNIT 1814